Check for updates

REVIEW

REVISED Novel antifungal agents in clinical trials [version 2; peer review: 2 approved]

Samantha E. Jacobs [iD]1, Panagiotis Zagaliotis[2], Thomas J. Walsh [iD]2,3

1Division of Infectious Diseases, Icahn School of Medicine, New York, NY, 10029-5674, USA
2Transplantation-Oncology Infectious Diseases Program, Division of Infectious Diseases, Department of Medicine, Weill Cornell Medicine, New York, NY, 10065, USA
3Departments Pediatrics and Microbiology & Immunology, Weill Cornell Medicine, New York, NY, 10065, USA

Abstract

Invasive fungal diseases due to resistant yeasts and molds are an important and increasing public health threat, likely due to a growing population of immunosuppressed hosts, increases in antifungal resistance, and improvements in laboratory diagnostics. The significant morbidity and mortality associated with these pathogens bespeaks the urgent need for novel safe and effective therapeutics. This review highlights promising investigational antifungal agents in clinical phases of development: fosmanogepix, ibrexafungerp, rezafungin, encochleated amphotericin B, oteseconazole (VT-1161), VT-1598, PC945, and olorofim. We discuss three first-in-class members of three novel antifungal classes, as well as new agents within existing antifungal classes with improved safety and tolerability profiles due to enhanced pharmacokinetic and pharmacodynamic properties.

Open Peer Review

Reviewer Status ✓ ✓

	Invited Reviewers	
	1	**2**
version 2 (revision) 12 Jan 2022		✓ report
version 1 28 Jun 2021	✓ report	? report

1. **Charalampos Antachopoulos** [iD], Aristotle University, Thessaloniki, Greece

2. **Shahram Mahmoudi** [iD], Iran University of Medical Sciences, Tehran, Iran

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Samantha E. Jacobs (samantha.jacobs1@mssm.edu)

Author roles: Jacobs SE: Writing – Review & Editing; **Zagaliotis P**: Writing – Review & Editing; **Walsh TJ**: Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing

How to cite this article: Jacobs SE, Zagaliotis P and Walsh TJ. **Novel antifungal agents in clinical trials [version 2; peer review: 2 approved]** F1000Research 2022, **10**:507 https://doi.org/10.12688/f1000research.28327.2

First published: 28 Jun 2021, **10**:507 https://doi.org/10.12688/f1000research.28327.1

> **REVISED** **Amendments from Version 1**
>
> We have specified the in vitro activity of fosmanogepix to the species level including representative MEC values. We have included data on the in vitro activity of ibrexafungerp and rezafungin against Candida parapsilosis in comparison with other Candida species. For fosmanogepix, ibrexafungerp, rezafungin, and olorofim, we have created an additional table to highlight the key PK/PD indices associated with therapeutic outcome in experimental animal models.
>
> **Any further responses from the reviewers can be found at the end of the article**

Introduction

Invasive fungal diseases (IFDs) are a growing public health concern in an expanding population of immunocompromised hosts[1]. Indeed, attributable mortality may still approach 90% in the most vulnerable patients infected with highly-resistant pathogens[1]. Three classes of antifungal drugs are currently available for prevention and treatment of IFDs: triazoles, polyenes, and echinocandins. However, use of these agents is often hampered by drug toxicity, drug-drug interactions, and lack of oral formulation. Furthermore, novel therapeutic options are needed due to increasing rates of antifungal resistance and increasing IFDs due to emerging pathogens, many of which are resistant to approved antifungal agents. Herein, we review the antifungal pipeline for agents in clinical phases of development. We give particular attention to investigational drugs with novel mechanisms targeting cellular and biochemical pathways.

Agents targeting the cell wall
Fosmanogepix

Mechanism of action. Glycosylphosphatidylinositol (GPI)-anchored mannoproteins are one of the major cell wall components of fungi. Inhibition of GPI-anchored protein biosynthesis therefore has the potential to compromise cell wall integrity and restrict fungal growth. Fosmanogepix (previously APX001 and E1210; Eisai Company, Japan) is a first-in-class antifungal prodrug that inhibits the fungal Gwt1 (GPI-anchored wall protein transfer 1) gene that encodes a new acyltransferase involved in an early step of the GPI post-translational biosynthetic pathway[2]. Fosmanogepix undergoes rapid and complete metabolism by systemic phosphatases to its active moiety, manogepix. The chemical structure, mechanism of action, spectrum of activity, clinical trials status, and potential advantages of fosmanogepix and other investigational antifungal agents included in this review are provided in Table 1.

Activity in vitro and in vivo. Fosmanogepix has broad-spectrum activity against a range of yeasts and molds. Potent *in vitro* activity is demonstrated against most *Candida* species with the exception of *Candida krusei*[2]. Fosmanogepix also shows *in vitro* activity against fluconazole-resistant *Candida* species, including *C. auris,* as well as echinocandin-resistant *C. albicans* and *C. glabrata* with *fks* mutations[2–5]. Among 16 *C. auris* isolates from Europe and Asia, fosmanogepix demonstrated a minimum inhibitory concentration (MIC) required to inhibit growth
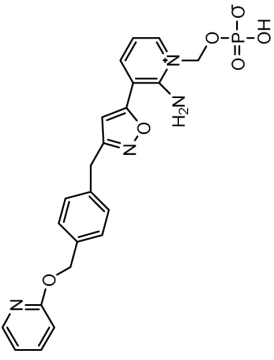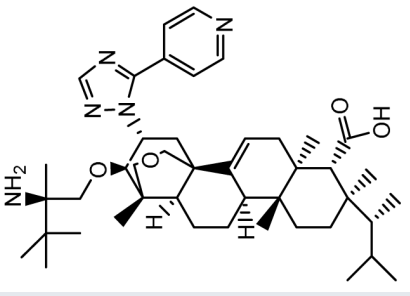
of 90% of organisms (MIC_{90}) value that was 8-fold lower than that of anidulafungin, the next most active agent. Highly potent *in vitro* activity was also observed in six pan-resistant *C. auris* isolates from New York (MIC range 0.008 μg/mL to 0.015 μg/mL)[6]. Furthermore, in a neutropenic mouse model of disseminated *C. auris*, treatment with fosmanogepix led to significantly improved survival and decreased fungal burden in brain tissue as compared to anidulafungin[5]. Fosmanogepix also was shown to have efficacy in treatment of experimental *Candida* endophthalmitis and hematogenous meningoencephalitis[7].
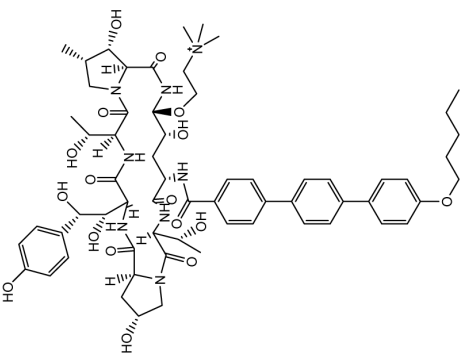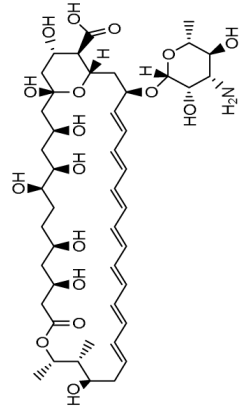
Fosmanogepix has activity against *Cryptococcus neoformans* and *C. gattii,* as well as *Coccidioides* species[8,9]. In mice with cryptococcal meningitis, the combination of fosmanogepix and fluconazole was observed to decrease fungal burden in a synergistic manner in brain tissue but not in lung tissue[9].
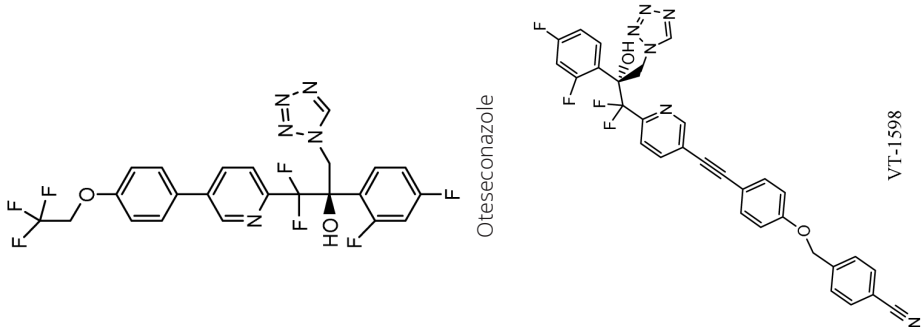
To determine the *in vitro* antifungal activity against moulds, the minimum effective concentration (MEC), rather than MIC, is determined. Amongst moulds, fosmanogepix has in vitro activity against a range of hyaline moulds including *Aspergillus spp.* (*A. fumigatus*, *A. flavus*., *A. niger*, *A. terreus*, *A. lentulus*, *A. ustus*), *Fusarium spp.* (*F. solani* and *F. oxysporum* species complex), *Scedosporium spp.* (*S. apiospermum*, *S. boydii*, *S. dehoogii*, *S. aurantiacum*), *Lomentospora prolificans,* and *Purpureocillium lilacinum*[2,3,10]. For example, against *Aspergillus spp.* (*A. fumigatus*, *Aspergillus* section *Flavi, Aspergillus* section *Terrei*, and *Aspergillus* section *Nigri*), fosmanogepix displayed a 50% minimal effective concentration (MEC_{50}) of 0.015 μg/ml; MEC_{90} of 0.03 μg/ml[3]. Fosmanogepix also exerted potent antifungal activity against *Scedosporium apiospermum* (MEC_{90} 0.12 μg/ml), *Scedosporium aurantiacum* (MEC_{50} 0.06 μg/ml), and *Scedosporium (Lomentospora) prolificans* (MEC_{90} 0.12 μg/ml), as well as *Fusarium solani* (MEC_{90} 0.06 μg/ml) and *Fusarium oxysporum* (MEC_{90} 0.25 μg/ml)[10]. These organisms pose formidable therapeutic challenges, particularly in immunocompromised patients[11]. In immunocompromised mouse models of invasive pulmonary aspergillosis, hematogenously disseminated fusariosis, and pulmonary scedosporiosis, fosmanogepix demonstrated improved survival and tissue clearance versus placebo; whereas, comparable outcomes were observed between mice treated with fosmanogepix and posaconazole (*Aspergillus*-infected mice) or high dose liposomal amphotericin B (*Fusarium*- and *Scedosporium*-infected mice)[12,13]. Fosmanogepix also has moderate activity against fungi in the order Mucorales (MIC ranges of 1 to 8 μg/mL)[2]. Against *Rhizomucor* and *Rhizopus spp.*, MEC ranges of 4 to >8 μg/mL are observed *in vitro*[3]. In a mouse model of pulmonary mucormycosis with two strains of *Rhizopus arrhizus* [minimum effective concentration (MEC) values of 0.25μg/mL and 4 μg/mL], fosmanogepix lead to improved survival and reduced lung and kidney fungal burden compared to placebo and similar outcomes as compared to isavuconazole[14].
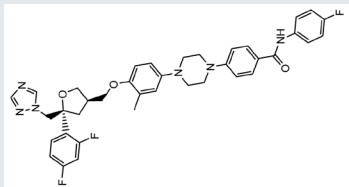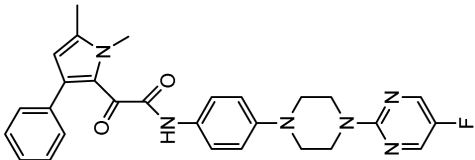
Pharmacokinetics/pharmacodynamics. Fosmanogepix is available in oral and intravenous (IV) formulations, achieving more than 90% bioavailability in humans. In rats and monkeys administered fosmanogepix via oral or IV route, rapid and extensive absorption to most tissues including lung, brain, liver,

Table 1. Novel investigational antifungal agents in clinical trials.

Class	Novel agent	Mechanism of action	Spectrum of activity	Completed/ongoing phase 2 and 3 clinical trials	Potential advantages
Glycosylphos-phatidylinositol (GPI) inhibitors	Fosmanogepix (APX001)	Inhibits the fungal enzyme Gwt1 to disrupt GPI-anchor post-translational protein modification	*Candida* spp. except *C. krusei* *Cryptococcus* spp. *Aspergillus* spp. *Fusarium* spp. *Scedosporium* spp. *Lomentospora prolificans* *Purpureocillium lilacinum* *Rhizopus arrhizus* *Coccidioides* spp.	<u>Ongoing</u> • Treatment of IFIs due to *Aspergillus* spp or rare moulds (NCT04240886) • Treatment of candidemia or invasive candidiasis due to *C. auris* (NCT04148287) • Treatment of candidemia in non-neutropenic patients (NCT03604705)	Broad spectrum and active against highly resistant fungi
Triterpenoids	Ibrexafungerp (SCY-078)	Inhibits (1(3)- β-D-glucan synthase	*Candida* spp. including echinocandin-resistant *C. glabrata* and *C. auris* *Aspergillus* spp. *Paecilomyces variotii* *Pneumocystis jirovecii*	<u>Completed</u> • Step-down therapy for candidemia and/or invasive candidiasis (NCT02244606) • Treatment of acute VVC (DOVE, NCT03253094; VANISH-303, NCT03734991; NCT02679456) <u>Ongoing</u> • Treatment in patients with refractory or intolerant fungal diseases (FURI, NCT03059992) • Ibrexafungerp and voriconazole combination for treatment of invasive pulmonary aspergillosis (NCT03672292) • Treatment of *Candida auris* infection (CARES, NCT03363841) • Prevention of recurrent VVC (CANDLE, NCT04029116) • Treatment of acute VVC (Vanish 306, NCT03987620)	• Active against resistant *Candida* species • First orally bioavailable inhibitor of (1(3)- β-D-glucan synthase • Combination therapy against invasive aspergillosis • Oral fungicidal therapy against *Candida* spp., including step-down for candidemia

Class	Novel agent	Mechanism of action	Spectrum of activity	Completed/ongoing phase 2 and 3 clinical trials	Potential advantages
Echinocandins	Rezafungin (CD101)	Inhibits (1(3)- β-D-glucan synthase	*Candida* spp. *Aspergillus* spp. *Pneumocystis jirovecii*	Completed • Treatment of candidemia and/or invasive candidiasis with fluconazole stepdown (STRIVE, NCT02734862) • Treatment of acute moderate to severe VVC (RADIANT, NCT02733432) Ongoing • Treatment of candidemia and/or invasive candidiasis (ReSTORE, NCT03667690) • Prevention of invasive fungal disease in patients undergoing allogeneic HCT (ReSPECT, NCT04368559)	• Long half-life allows once weekly dosing; • Not hepatotoxic • Activity may prevent *Pneumocystis* pneumonia
Polyenes	Encochleated amphotericin B (MAT2203)	Binds to ergosterol to form pores in fungal cell membrane	*Candida* spp. *Aspergillus* spp. *Cryptococcus* spp.	Completed • Treatment of VVC (NCT02971007) Ongoing • Treatment of refractory mucocutaneous candidiasis (NCT02629419) • Treatment of cryptococcal meningitis in HIV-infected patients (EnACT, NCT04031833)	• Oral formulation • Less toxicity than deoxycholate and lipid formulations of amphotericin B

Class	Novel agent	Mechanism of action	Spectrum of activity	Completed/ongoing phase 2 and 3 clinical trials	Potential advantages
Tetrazoles	Oteseconazole (VT-1161), VT-1598 Oteseconazole VT-1598	Inhibition of lanosterol 14-alpha-demethylase enzyme to disrupt ergosterol synthesis	*Candida* spp. including fluconazole- and echinocandin-resistant *C. glabrata* *Cryptococcus* spp. *Coccidioides* spp. *Histoplasma capsulatum* *Blastomyces dermatitidis* *Aspergillus* spp. *Rhizopus arrhizus*	Completed (Oteseconazole) • Treatment of toenail onychomycosis (NCT02267356) • Treatment of recurrent VVC (NCT02267382) • Treatment of acute vaginal candidiasis (NCT01891331) Ongoing (Oteseconazole) • Treatment of recurrent VVC (NCT02267382, NCT03562156, NCT03561701, NCT03840616) • Treatment of tinea pedis (NCT01891305)	• Fungal-specific enzyme target leads to fewer drug-drug interactions • Broad spectrum against yeasts, endemic fungi, and moulds (VT-1598)

Class	Novel agent	Mechanism of action	Spectrum of activity	Completed/ongoing phase 2 and 3 clinical trials	Potential advantages
Triazoles	PC945	Inhibition of lanosterol 14-alpha-demethylase enzyme to disrupt ergosterol synthesis	*Candida* spp. including fluconazole-resistant *C. glabrata*, *C. krusei* and *C. auris* *Cryptococcus* spp. *Trichophyton rubrum* *Aspergillus fumigatus* and *A. terreus*	None	• Inhaled delivery • Activity against azole-resistant *Aspergillus fumigatus*
Orotomides	Olorofim (F901318)	Inhibits the pyrimidine biosynthesis enzyme dihydroorotate dehydrogenase	*Aspergillus* spp. *Scedosporium* spp. *Lomentospora prolificans* *Fusarium* spp. *Histoplasma capsulatum* *Blastomyces dermatitidis* *Coccidioides* spp.	<u>Ongoing</u> • Treatment of IFIs due to resistant fungi (FORMULA-OLS, NCT03583164)	• Active against highly-resistant moulds

IFI, invasive fungal infection; VVC, vulvovaginal candidiasis

kidney, and eye were observed. Elimination was primarily biliary (rats) and fecal (monkeys)[15]. The 24-hour free-drug area under the concentration-time curve (AUC)/MIC ratio ($fAUC_{0-24}$/MIC) is the PK/PD index that best correlates with efficacy in a neutropenic murine disseminated candidiasis model (Table 2)[16]. In phase 1 studies, plasma exposure to fosmanogepix was linear and dose proportional with a half-life of approximately 2.5 days[17]. Fosmanogepix was well-tolerated; there was no dose-limiting toxicity, and the most common adverse event was headache[17]. A phase 1b study of fosmanogepix safety and pharmacokinetics in patients with acute myeloid leukemia is completed, but results are not yet available (NCT03333005).

Clinical development. Clinical development of fosmanogepix has thus far focused on its role in the treatment of infections due to *Candida* spp., *Aspergillus* spp., and rare moulds. The U.S. Food and Drug Association (FDA) has granted Fast Track, Qualified Infectious Disease Product (QIDP), and orphan drug designation to fosmanogepix for the following indications: treatment of invasive candidiasis, invasive aspergillosis, scedosporiosis, fusariosis, mucormycosis, cryptococcosis, and coccidioidomycosis. Phase 2 trials are ongoing for the treatment of IFDs caused by *Aspergillus* spp. or rare moulds (NCT04240886), treatment of candidemia or invasive candidiasis due to *C. auris* (NCT04148287), and treatment of candidemia in non-neutropenic patients (NCT03604705).

Ibrexafungerp

Mechanism of action. Similar to the echinocandins, ibrexafungerp (previously MK-3118 and SCY-078; Scynexis, Jersey City, NJ, USA) disrupts fungal cell wall synthesis through inhibition of (1→3)-β-D-glucan synthase with fungicidal activity against *Candida* spp. However, ibrexafungerp is structurally distinct as a semisynthetic derivative of the naturally occurring hemiacetal triterpene glycoside enfumafungin that incorporates a pyridine triazole at position 15 of the core phenanthropyran carboxylic acid ring system and a 2-amino- 2,3,3-trimethyl-butyl ether at position 14 to enhance its antifungal potency and pharmacokinetic properties; thus, representing the first compound in the novel class of triterpenoid antifungals[18]. As compared to echinocandins, ibrexafungerp has distinct advantages of oral bioavailability, broad activity against pan-resistant *C. auris,* and maintaining activity against most echinocandin-resistant *Candida* spp.

Activity in vitro and in vivo. Ibrexafungerp exhibits potent fungicidal activity against *Candida* species, including *C. glabrata* and multiple clades of *C. auris*[19–21]. The *in vitro* activity of ibrexafungerp against *C. parapsilosis*, which is known to have elevated echinocandin MICs, is comparable to or improved from that of the echinocandins[22]. The modal MIC of ibrexafungerp against *C. parapsilosis* is also similar to the modal MIC observed against other common *Candida* species causing clinical disease, *C. albicans*, *C. glabrata*, *C. tropicales*, and *C. krusei*[23]. Notably, ibrexafungerp retains *in vitro* activity against most echinocandin-resistant *C. glabrata* with *fks* mutations (MIC mode, MIC_{50}, and MIC_{90} of 0.25μg/mL, 0.25μg/mL, and 1.0μg/mL, respectively)[22]. Amongst *C. auris* isolates with echinocandin resistance or pan-antifungal resistance, ibrexafungerp demonstrates MIC ranges from 0.25μg/mL to 1μg/mL and 0.12μg/mL to 1μg/mL, respectively[20,24,25]. In addition, *C. auris* biofilms treated with ibrexafungerp show reduced metabolic activity and thickness as compared to untreated control biofilms[26].

Ibrexafungerp has fungistatic activity against *Aspergillus* species (MEC range <0.06μg/mL to 4μg/mL)[27]. The combination of ibrexafungerp with voriconazole, amphotericin B, or isavuconazole demonstrates *in vitro* synergy against wild-type

Table 2. Key Pharmacodynamic Indices Associated with Therapeutic Outcome in Experimental Model Systems of Invasive Candidiasis or Invasive Aspergillosis.

Antifungal agent	Animal model	Organism	Key PD index	Reference(s)
Fosmanogepix	Murine	*C. albicans* *C. glabrata* *C. auris*	AUC/MIC	15
Ibrexafungerp	Murine	*C. albicans* *C. glabrata* *C. parapsilosis*	AUC/MIC	18,28
Rezafungin	Murine	*C. albicans* *C. glabrata* *C. parapsilosis*	AUC/MIC	29
Olorofim	Murine	*A. flavus* *A. fumigatus*	C_{min}/MIC	30,31

PD, pharmacodynamic; AUC, area under the concentration-time curve; MIC, minimum inhibitory concentration, C_{min}, minimum plasma concentration

There are insufficient PK/PD data for assignment of a PD index for encochleated amphotericin B, oteseconazole, and PC945.

(WT) *Aspergillus* species but not against azole-resistant strains[27]. Little *in vitro* activity is observed with ibrexafungerp against the Mucorales and non- *Aspergillus* hyaline moulds (*Fusarium* spp, *Scopulariopsis* spp, *Lomentospora prolificans*) with the exception of *Paecilomyces variotii* (MEC <0.02μg/mL to 0.03μg/mL)[32]. However, synergistic interaction between ibrexafungerp and isavuconazole is observed *in vitro* against *Cunninghamella bertholletiae*, *S. apiospermum*, *F. solani* and *F. oxysporum*; whereas, indifference or antagonism are observed with *Mucor circinelloides* and *Rhizopus* species, respectively[33].

In a murine invasive candidiasis model with WT and echinocandin-resistant (ER) *C. glabrata*, ibrexafungerp significantly reduced kidney fungal burden in both groups as compared to placebo. In contrast, caspofungin administered by intraperitoneal injection reduced fungal burden in the WT group but not the ER group[34]. Reduced tissue fungal burden and improved survival with ibrexafungerp versus control also were observed in immunocompromised mice with disseminated *C. auris*[35].

In a murine model of disseminated aspergillosis, treatment with ibrexafungerp led to significant reduction in *Aspergillus* kidney burden and serum galactomannan (GM) levels and improved survival as compared to control[36]. This *in vivo* activity of ibrexafungerp was observed in both wild type and azole-resistant isolates of *A. fumigatus*.

The combination of ibrexafungerp and isavuconazole also demonstrates synergy in a neutropenic rabbit model of experimental invasive pulmonary aspergillosis. As compared to isavuconazole alone, mice treated with ibrexafungerp and isavuconazole had significantly improved survival, decreased pulmonary infarct scores, and diminished serum GM levels[37].

Ibrexafungerp is also efficacious in a murine model of *Pneumocystis murina* pneumonia, in which reductions in asci burden and improvements in survival were similar to those of trimethoprim-sulfamethoxazole and significantly better than in untreated controls[38].

Pharmacokinetics/pharmacodynamics. Ibrexafungerp is orally bioavailable and highly protein bound (~99.6%) in humans. The maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) increase approximately 20% with high fat meals[39]. It has a large volume of distribution in mice, rats, and dogs. Concentration in multiple tissues including liver, spleen, lungs, bone marrow, kidney, and skin exceeds that of plasma. However, there is low distribution to central nervous system (CNS) tissue[40]. In rats, approximately 90% of drug is eliminated in feces and bile, and 1.5% eliminated in urine[40]. The PK/PD index that best correlates with efficacy in a murine models of disseminated candidiasis is AUC/MIC (Table 2)[18,41]. Ibrexafungerp is a substrate of CYP3A and P-glycoprotein, though it neither induces or nor inhibits CYP3A. When ibrexafungerp and tacrolimus are co-administered, there is a 1.4-fold increase in AUC and no change in tacrolimus C_{max}[42]. Thus, initial tacrolimus dose adjustment is not needed when co-administered with ibrexafungerp.

Clinical development. Ibrexafungerp will likely play an important role in management of invasive candidiasis due to WT and resistant *Candida* species and invasive aspergillosis; the drug has received QIDP and orphan drug designations for both indications.

In a phase 2 open-label, randomized study, 27 patients with invasive candidiasis were randomized to receive step-down therapy to one of three treatment arms: two dosing regimens of ibrexafungerp (1000mg loading dose followed by 500mg daily or 1250mg loading dose followed by 750mg daily) or standard of care (SOC) following initial echinocandin therapy. Similar rates of adverse events were observed across study arms; study-drug related treatment-emergent adverse events were reported in two patients (vomiting and diarrhea) and did not require drug discontinuation. There was no difference in favorable global response rates (clinical and microbiologic): 86%, 71%, and 71% in the ibrexafungerp 750mg, ibrexafungerp 500mg, and SOC arms, respectively, although the study was not powered to detect statistical superiority[28].

A phase 3 open-label, single arm study of ibrexafungerp in patients with refractory or intolerant fungal diseases is ongoing (FURI; NCT03059992). An interim analysis was performed in 20 patients with proven or probable invasive candidiasis (N=11) or severe mucocutaneous candidiasis (N=9). Eleven (55%) patients achieved a complete or partial response and 6 (30%) had stable disease. The most common treatment-related adverse events were gastrointestinal[43]. Target enrollment is 200 patients, and the estimated study completion date is December 2021.

Ibrexafungerp has also been studied for the treatment of vulvovaginal candidiasis (VVC). Day 10 and day 25 clinical cure and mycological eradication rates were similar or improved with ibrexafungerp 300mg twice daily × 2 doses compared to fluconazole 150mg × 1 dose. Diarrhea was the most common adverse event in the ibrexafungerp arm, observed in 10% of subjects[44]. An new drug application has since been submitted for treatment of VVC.

Other ongoing clinical trials include a multicenter, randomized, double-blind study to evaluate the efficacy and safety of ibrexafungerp and voriconazole in patients with invasive pulmonary aspergillosis (NCT03672292). Ibrexafungerp is also in open-label clinical trials in India and the United States for treatment of *Candida auris* infection (CARES; NCT03363841). Thus far, outcomes of two patients enrolled in the CARES Study have been reported; both had *C. auris* bloodstream infections and were successfully treated with ibrexafungerp[45].

Combination antifungal therapy with a cell wall active agent and an antifungal triazole is a potentially important strategy in treatment of invasive aspergillosis [33]. Ibrexafungerp may develop a key role in combination antifungal therapy with an antifungal triazole in treatment of invasive aspergillosis. Simultaneous administration of an orally administered triazole and ibrexafungerp may allow patients to receive the potential

therapeutic benefit of combination therapy in treatment of invasive pulmonary aspergillosis on an ambulatory basis.

Rezafungin

Mechanism of action. Rezafungin (formerly SP3025 and CD101; Cidara Therapeutics, San Diego, CA, USA) is a novel agent in the echinocandin antifungal drug class that inhibits (1→3)-β-D-glucan synthesis. Rezafungin is a structural analogue of anidulafungin but it is differentiated by a choline moiety at the C5 ornithine position, conferring increased stability and solubility[46]. Due to its long half-life, rezafungin has the advantage of once weekly dosing as compared to other drugs within the echinocandin class that require daily dosing.

Activity in vitro and in vivo. Rezafungin has potent *in vitro* activity that mirrors that of other echinocandins against WT and azole-resistant *Candida* species, as well as WT and azole-resistant *Aspergillus* species[47–49]. Similar to other echinocandins, rezafungin has higher MICs (MIC_{50} 1 μg/mL/MIC_{90} 2 μg/mL) against *C. parapsilosis* compared to other common *Candida* species.

In immunocompromised mouse models of *C. albicans* and *A. fumigatus* infection, decreased fungal tissue burden and improved 10-day survival, respectively, were observed with rezafungin as compared to controls[50]. Rezafungin also had activity in a mouse model of disseminated *C. auris*, leading to decreased fungal tissue burden as compared to amphotericin B and control[51]. Furthermore, rezafungin was efficacious as prophylaxis against *Pneumocystis* in a mouse model, supporting its potential for development for prevention of *Pneumocystis* pneumonia in immunocompromised hosts[52].

Pharmacokinetics/pharmacodynamics. Similar to other echinocandin drugs, rezafungin demonstrates a concentration-dependent pattern of fungicidal activity. Therefore, a front-loaded dosing regimen conferring higher plasma drug exposure may theoretically enhance pathogen killing and raise the barrier to drug resistance[53]. In animal models, the AUC/MIC correlates best with therapeutic outcome[54] (Table 2). In phase 1 ascending dose studies evaluating single doses up to 400mg and multiple doses up to 400mg once weekly for 3 weeks in healthy adults, rezafungin demonstrated dose-proportional plasma exposures, long half-life (approximately 80 hours after the first dose and 152 hours after the third dose), and minimal renal excretion[55]. The C_{max} ranged from ~5 μg/mL with the 100mg dose to ~22 to 30 μg/mL with the 400mg dose. Overall, rezafungin was well tolerated. There were no serious adverse events; most adverse events were mild and gastrointestinal (constipation and nausea). Mild infusion reactions characterized by nausea, flushing, and chest discomfort were also observed, most often with the third dose of 400mg of rezafungin. These reactions resolved within minutes without drug interruption or discontinuation.

Clinical development. Rezafungin has received U.S. FDA QIDP and Fast Track designations for prevention of invasive fungal infections as well as QIDP, Fast Track, and orphan drug designations for treatment of invasive candidiasis.

A phase 2 multicenter, randomized, double-blinded trial in 207 adult patients with candidemia and/or invasive candidiasis compared the efficacy and safety of treatment with rezafungin versus caspofungin with fluconazole stepdown once clinically stable (STRIVE; NCT02734862)[56]. Patients were randomized to one of three treatment arms: rezafungin 400mg once weekly, rezafungin 400mg on week 1, then 200mg weekly, and caspofungin 70mg loading dose followed by 50mg daily for ≤4 weeks. The primary endpoint was overall cure, defined as resolution of signs of candidemia or invasive candidiasis and mycological eradication at day 14. The study was not designed for statistical comparison of the efficacy assessment, but overall cure rates and 30-day mortality, respectively, were similar across groups: rezafungin 400mg weekly (60.5% and 15.8%), rezafungin 400mg/200mg weekly (76.1% and 4.4%), and caspofungin (67.2% and 13.1%). In patients with candidemia, blood cultures cleared in 19.5 and 22.8 hours in the rezafungin and caspofungin groups, respectively. Rezafungin was also well-tolerated. The most common adverse events – hypokalemia, diarrhea, and vomiting – were observed in similar proportions of patients in the rezafungin and caspofungin groups. Study drug-related serious adverse events occurred in one patient in each rezafungin group and two patients in the caspofungin group.

Based on the promising results of STRIVE, a phase 3 clinical trial of rezafungin versus caspofungin for treatment of candidemia and invasive candidiasis is ongoing (ReSTORE; NCT03667690). Another ongoing phase 3 trial compares rezafungin to standard of care for prevention of IFD due to *Candida* spp., *Aspergillus* spp., and *Pneumocystis* in patients undergoing allogeneic hematopoietic cell transplantation (ReSPECT; NCT04368559). The primary outcome is fungal-free survival at Day 90. In both phase 3 trials, rezafungin is dosed 400mg for the first week followed by 200mg once weekly.

Agents targeting the cell membrane
Encochleated Amphotericin B (MAT2203)

Mechanism of action and pharmacology. Amphotericin B (AmB), a polyene antifungal agent, disrupts fungal cell wall synthesis by binding to ergosterol to form pores that allow leakage of intracellular contents, resulting in potent fungicidal activity against a wide range of yeasts and moulds. However, AmB and its lipid formulations are only available via intravenous injection due to low solubility, a tendency to self-aggregate in aqueous media, and low permeability[29]. Encochleated AmB (CAmB; Matinas BioPharma, Bedminster, NJ, USA) is a novel formulation that allows for oral administration with reduced toxicity. Cochleates form a multilayered structure composed of a negatively charged lipid (phosphatidylserine) and a divalent cation (calcium). This structure protects AmB from degradation within the gastrointestinal tract[57]. AmB is released to the fungus only when the cochleates interact with the target cells and subsequently destabilize in the setting of low intracellular calcium concentration.

Activity in vitro and in vivo. Comparable *in vitro* activity against *Candida* spp. and *Aspergillus* spp. are observed with CAmB and deoxycholate AmB[58,59]. CAmB has been successfully

administered in immunocompromised mouse models of disseminated *C. albicans* infection and disseminated aspergillosis. In both studies, oral CAmB and intraperitoneal deoxycholate amphotericin B demonstrated similar improvement in survival and reduction in tissue fungal burden as compared to untreated control animals[58,60]. Furthermore, CAmB was evaluated in a mouse model of cryptococcal meningoencephalitis where CAmB plus flucytosine had similar efficacy to parenteral AmB plus flucytosine and demonstrated potent activity[61].

Pharmacokinetics/pharmacodynamics. A single dose of CAmB demonstrates extensive tissue distribution and penetration into target tissues in animal models[62]. In a phase 1 study in healthy adults evaluating escalating doses of 200, 400, and 800mg, CAmB was well tolerated at doses of 200mg and 400mg. The most common adverse events were gastrointestinal, occurring in 6%, 38%, and 56% of patients in the 200mg, 400mg, and 800mg groups, respectively. There were no serious adverse events or renal toxicity observed. Dose-dependent increases in C_{max} and AUC were observed, comparable to those of animal toxicity studies[63].

Clinical development. A phase 2a single-arm study of CAmB for refractory mucocutaneous candidiasis is ongoing (NCT02629419). Preliminary results indicate that all enrolled patients met the primary endpoint of ≥ 50% improvement in clinical signs and symptoms. CAmB was well tolerated at 400mg and 800mg with no observed renal or hepatic toxicity. In a phase 2 study of CAmB 200mg and 400mg and fluconazole 150mg for VVC in 137 patients, lower rates of clinical cure and more adverse events were observed with CAmB 200mg and 400mg as compared to fluconazole (NCT02971007). There were no serious adverse events[64]. Phase 1 and 2 studies of CAmB for treatment of cryptococcal meningitis in HIV-infected patients in Uganda are ongoing (EnACT; NCT04031833). CAmB has FDA-granted Fast Track, QIDP, and orphan drug designations for treatment of invasive candidiasis and aspergillosis, prevention of IFDs in patients on immunosuppressive therapy, and treatment of cryptococcosis.

Oteseconazole (VT-1161), VT-1598, VT-1129

Mechanism of action. Second-generation triazole antifungal agents, such as voriconazole, are highly effective against a range of yeasts and moulds; however, they are associated with significant drug-drug interactions due to off-target inhibition of human cytochrome P450 enzymes. Oteseconazole (VT-1161), VT-1598, and VT-1129 (Mycovia Pharmaceuticals, Inc., Durham, NC, USA) are next-generation azoles in which selective inhibition of the fungal enzyme CYP51 is more readily achieved by replacing the 1-(1,2,4-triazole) metal-binding group with a tetrazole[65].

Activity in vitro and in vivo. Oteseconazole, VT-1598, and VT-1129 have potent *in vitro* activity against *Cryptococcus* spp. and *Candida* spp. including *C. krusei* and fluconazole- and echinocandin-resistant *C. glabrata*[66,67]. VT-1598 has the broadest spectrum, which includes *C. auris*, moulds (*Aspergillus* spp. and *Rhizopus* spp.) and endemic dimorphic fungi (*Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides posadasii*,

and *C. immitis*)[68–70]. In murine models of CNS coccidioidomycosis, VT-1598 treatment leads to improved survival and reduced fungal burden in brain tissue as compared to fluconazole. Oteseconazole has similarly demonstrated efficacy in murine models of pulmonary and CNS coccidioidomycosis as well as disseminated mucormycosis due to *Rhizopus arrhizus* var. *arrhizus*[71,72].

Clinical development. The FDA has granted QIDP, fast track, and orphan drug designation to VT-1598 for the treatment of coccidioidomycosis (Valley fever)[73]. VT-1598 is in phase 1 studies (NCT04208321). Oteseconazole is in phase 3 clinical trials for treatment of recurrent vaginal candidiasis (NCT02267382, NCT03562156, NCT03561701) after demonstrating safety and efficacy in a phase 2 study and has FDA QIDP and Fast-Track designations for this indication[74]. A phase 2 trial for toenail onychomycosis demonstrated higher week 48 cure rates with oteseconazole (32 to 42%) versus placebo (0%) (NCT02267356)[75]. In these completed trials, oteseconazole was well-tolerated with no evidence of hepatotoxicity or QT prolongation.

PC945

Mechanism of action. As compared to systemic therapy, aerosolized delivery of antifungal agents to the lung results in higher concentrations in epithelial lining fluid and bronchoalveolar lavage fluid; however, for successful activity, drug levels must be sustained in lung tissues with minimal systemic absorption[76]. PC945 (Pulmocide, London, United Kingdom) is a novel triazole antifungal agent that is being developed specifically for inhaled administration for treatment and prevention of invasive fungal infections of the sinopulmonary tract. The structure of PC945 is similar to but distinct from that of posaconazole. The structures are similar in having 2,4-difluorophenyl and 1H-1,2,4-triazole substitutions on the asymmetric carbon atom. However, PC945 differs structurally in having a central oxolane ring (in place of the dioxalane ring) and a long hydrophobic 3-ylmethoxy-3-methylphenyl[piperazin-1-yl]-N-(4-fluorophenyl)benzamide substitution. This hydrophobic moiety likely contributes to the sustained intrapulmonary concentrations of PC945.

Activity in vitro and in vivo. PC945 has *in vitro* activity against azole-susceptible *A. fumigatus* [median MIC 0.031µg/mL (IQR 0.02 – 0.031µg/mL)] and most azole-resistant *A. fumigatus*[77]. Activity against *A. terreus* is comparable to posaconazole and more potent than that of voriconazole; however, PC945 has poor *in vitro* activity against *A. flavus* and *A. niger*. PC945 lacks activity against most Mucorales; although a MIC 2µg/mL was observed for *Rhizopus oryzae*[77]. Against *Candida albicans* (both azole-susceptible and azole-resistant strains), *C. glabrata*, and *C. krusei*, PC945 is generally more active than voriconazole and shares equal potency with posaconazole[77]. Using a global collection of 50 clinical *Candida auris* isolates, PC945 had more potent *in vitro* activity than posaconazole, voriconazole, and fluconazole [PC945 GM MIC (MIC_{50}, MIC_{90}): 0.14µg/mL (0.13, 1µg/mL)][78].

An *in vitro* model of the human alveolus has been developed to better understand the pathogenesis of invasive pulmonary

aspergillosis and the relationship between the kinetics of GM and outcomes of antifungal therapy[79]. Using this model, combination therapy with apical PC945 and basolateral posaconazole or voriconazole for azole-susceptible and azole-resistant *A. fumigatus* demonstrated synergistic activity as compared to either agent alone[80].

The therapeutic potential of intranasal PC945 has been investigated in transiently neutropenic mice with invasive pulmonary aspergillosis. Intranasal PC945 leads to reduced concentrations of GM in bronchoalveolar lavage fluid (BALF) and serum and improved survival as compared to controls, and reduced GM concentration and similar survival as compared to intranasal posaconazole[77,81]. Combination therapy with intranasal PC945 and oral posaconazole was also evaluated in immunocompromised neutropenic mice with azole-susceptible *A. fumigatus* infection. Suboptimal dosages of PC945 and posaconazole were administered simultaneously, (i.e., doses at which either agent alone led to zero survival at Day 7), and Day 7 survival improved to 83%[80]. As a potential prophylactic agent, PC945 was administered in the same *A. fumigatus*-infected mouse model from days -7 to +3 and days -1 to +3. Extended prophylaxis (days -7 to +3) yielded greater inhibition of fungal load in lung tissue and GM concentrations in BALF and serum as compared to shorter duration, suggesting that the antifungal effects of PC945 accumulated in the lung upon repeat dosing[81].

Pharmacokinetics/pharmacodynamics. Using the human alveolus, topical PC945 demonstrates sustained residency and antifungal activity in epithelial cells[80].

Clinical development. A phase 1 trial of PC945 in 29 healthy subjects and patients with mild asthma is completed; results are not yet available on clinicaltrials.gov (NCT02715570). A phase 3 study of PC945 for adults, who have limited or no alternative treatment options, for the treatment of invasive pulmonary aspergillosis as part of a combined antifungal regimen is planned to start in 2021.

In a report of two lung transplant recipients with bronchial anastomotic masses due to *A. fumigatus*, PC945, administered in combination with systemic antifungal agents, was well-tolerated, and clinical resolution of infection was observed[82].

Agents targeting nucleic acid metabolism
Olorofim
Mechanism of action. Olorofim (previously F910318, discovered by F2G Ltd, Australia), a member of the novel antifungal class, orotomides, is in an inhibitor of the pyrimidine biosynthesis fungal enzyme dihydroorotate dehydrogenase. Interruption of pyrimidine synthesis impairs nucleic acid production and leads to the arrest of hyphal extension[83].

Activity in vitro and in vivo. Olorofim is unique among existing antifungal agents in that it has no activity against *Candida* species. Rather, olorofim has potent activity *in vitro* against WT and azole-resistant *Aspergillus* spp., some other highly resistant

hyaline moulds, and *Coccidioides* spp.[84] Amongst 133 azole-resistant *A. fumigatus* isolates due to TR34/L98H,TR46/Y121F/T289A, *cyp51A*-associated point mutations, or unknown resistance mechanisms, MIC range was 0.031μg/mL to 0.125μg/mL, 0.062μg/mL to 0.25μg/mL, and 0.01μg/mL to 0.125μg/mL, respectively[85]. Several studies have also shown excellent activity *in vitro* against *Scedosporium* species (MIC_{50}/MIC_{90} 0.06/0.25μg/mL) and *L. prolificans* (MIC_{50}/MIC_{90} 0.12/0.2μg/mL) including biofilm formation by the latter[86–88]. The geometric mean MICs of olorofim were significantly lower for all *Scedosporium* species and *L. prolificans* compared with those of voriconazole, posaconazole, amphotericin B, and caspofungin[86]. Less *in vitro* data are available for *Fusarium* species, but susceptibility appears to be species-specific, with lower MICs observed for *F. proliferatum* than *F. solani* species complex and *F. dimerum*[89]. Olorofim has no activity against the Mucorales or the dematiaceous pathogen *Exophiala dermatitidis*[83,90].

In murine models of profound neutropenia and chronic granulomatous disease with disseminated and pulmonary aspergillosis, respectively, intraperitoneal administration of olorofim lead to significantly reduced serum GM levels and organ fungal DNA burden and improved survival as compared to controls[30]. In a murine model of acute sinopulmonary aspergillosis due to *A. flavus*, olorofim had comparable antifungal activity to posaconazole for the outcomes of decline in GM, histologic clearance of lung tissue, and survival[31].

Pharmacokinetics/pharmacodynamics. Olorofim is available in oral and IV formulations and demonstrates time-dependent antifungal activity[31,91]. Olorofim initially has a fungistatic effect on *Aspergillus* isolates but prolonged exposure is fungicidal[92]. Pharmacokinetic studies in mice have identified good distribution of olorofim to tissues including the kidney, liver, and lung, with lower levels of detection in the brain[83]. Olorofim exhibits time-dependent antifungal activity; the PK/PD index minimum inhibitory concentration (C_{min})/MIC strongly correlates with treatment outcome in murine models of invasive aspergillosis[30,31] (Table 2). In a phase 1 study of multiple doses of an immediate-release tablet (360mg daily for 10 days), steady state was reached within three days of dosing, and once attained, mean plasma trough levels were 1 to 2μg/mL and exceeded 0.7μg/mL in all subjects. There was evidence of enterohepatic recirculation. Olorofim was well-tolerated in all eight subjects with no serious adverse events and no subject withdrawn due to an AE. Drug-related adverse events included increased ALT (N=2), nausea and diarrhea (N=1), and dizziness (N=1)[93]. Olorofim is a weak inhibitor of CYP3A4[94].

Clinical development. Olorofim received designation from the U.S. FDA as a breakthrough therapy in 2019 and as an orphan drug in 2020. The European Medicines Agency Committee for Orphan Medicinal Products also granted orphan drug status to olorofim for the treatment of invasive aspergillosis and scedosporiosis in March 2019. A phase 2 clinical trial of olorofim for the treatment of IFDs due to resistant fungi including azole-resistant aspergillosis, scedosporiosis, and

lomentosporiosis is ongoing (FORMULA-OLS; NCT03583164) as is a phase 1 drug-drug interaction study with itraconazole and rifampicin (NCT04171739).

Conclusion

Despite significant advances in prevention, diagnosis, and management of IFDs over the past several decades, IFDs remain a formidable threat to immunocompromised hosts. In addition to strategies to augment host response and reduce immuno-suppression, novel therapeutics with potent fungicidal activity and low toxicity are urgently needed. We review investigational drugs in clinical phases of development, including three agents within three novel antifungal classes targeting the fungal cell wall and nucleic acid metabolism, fosmanogepix, olorofim, and ibrexafungerp. Fosmanogepix and olorofim are unique in their potent activity against highly-resistant molds for which we have few, if any, effective agents in our current antifungal armamentarium. Ibrexafungerp has selective advantage as an oral fungicidal therapy for *Candida* species including echinocandin-resistant *C. glabrata* and *C. auris*. Four other investigational agents within existing antifungal drug classes, rezafungin, CAmB, oteseconazole, and PC945, demonstrate enhanced pharmacokinetic and pharmacodynamic properties that importantly afford improved safety and tolerability profiles. Rezafungin, in particular, with its once weekly dosing, may facilitate outpatient management of patients needing an echinocandin for treatment or prophylaxis. Overall, we are optimistic that the current antifungal pipeline will expand our ability to provide safe and effective treatments to patients suffering from IFDs.

Data availability

No data is associated with this article.

References

1. Brown GD, Denning DW, Gow NAR, *et al.*: **Hidden killers: Human fungal infections.** *Sci Transl Med.* 2012; **4**(165): 165rv13.
   PubMed Abstract | **Publisher Full Text**

2. Miyazaki M, Horii T, Hata K, *et al.*: *In vitro* **activity of E1210, a novel antifungal, against clinically important yeasts and molds.** *Antimicrob Agents Chemother.* 2011; **55**(10): 4652–4658.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

3. Pfaller MA, Huband MD, Flamm RK, *et al.*: *In Vitro* **Activity of APX001A (Manogepix) and Comparator Agents against 1,706 Fungal Isolates Collected during an International Surveillance Program in 2017.** *Antimicrob Agents Chemother.* 2019; **63**(8): e00840-19.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

4. Wiederhold NP, Najvar LK, Fothergill AW, *et al.*: **The investigational agent E1210 is effective in treatment of experimental invasive candidiasis caused by resistant** *Candida albicans.* *Antimicrob Agents Chemother.* 2015; **59**(1): 690–692.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

5. Hager CL, Larkin EL, Long L, *et al.*: *In vitro* **and** *in vivo* **evaluation of the antifungal activity of APX001A/APX001 against Candida auris.** *Antimicrob Agents Chemother.* 2018; **62**(3): e02319-17.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

6. Zhu Y, Kilburn S, Kapoor M, *et al.*: *In Vitro* **Activity of Manogepix against Multidrug-Resistant and Panresistant Candida auris from the New York Outbreak.** *Antimicrob Agents Chemother.* 2020; **64**(11): e01124-20.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

7. Petraitis V, Petraitiene R, Bo B, *et al.*: **Efficacy of APX001 in treatment of Candida endophthalmitis and haematagenous meningoencephalitis in experimental non-neutropenic rabbit model.** In: *28th European Congress of Clinical Microbiology and Infectious Diseases.* Madrid, Spain; 2018: 7019.
   Reference Source

8. Viriyakosol S, Kapoor M, Okamoto S, *et al.*: **APX001 and other Gwt1 inhibitor prodrugs are effective in experimental Coccioides** *immitis* **pneumonia.** *Antimicrob Agents Chemother.* 2019; **63**(2): e01715-18.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

9. Shaw KJ, Schell WA, Covel J, *et al.*: *In Vitro* **and** *In Vivo* **Evaluation of APX001A / APX001 and Other Gwt1 Inhibitors against Cyptococcus.** *Antimicrob Agents Chemother.* 2018; **62**(8): e00523-18.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

10. Castanheira M, Duncanson FP, Diekema DJ, *et al.*: **Activities of E1210 and comparator agents tested by CLSI and EUCAST broth microdilution methods against** *Fusarium* **and** *Scedosporium* **species identified using molecular methods.** *Antimicrob Agents Chemother.* 2012; **56**(1): 352–357.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

11. Jacobs SE, Wengenack NL, Walsh TJ: **Non-** *Aspergillus* **Hyaline Molds: Emerging Causes of Sino-Pulmonary Fungal Infections and Other Invasive Mycoses.** *Semin Respir Crit Care Med.* 2020; **41**(1): 115–130.
    PubMed Abstract | **Publisher Full Text**

12. Gebremariam T, Alkhazraji S, Alqarihi A, *et al.*: **APX001 is effective in the treatment of murine invasive pulmonary aspergillosis.** *Antimicrob Agents Chemother.* 2019; **63**(2): e01713-18.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

13. Alkhazraji S, Gebremariam T, Alqarihi A, *et al.*: **Fosmanogepix (APX001) is effective in the treatment of immunocompromised mice infected with invasive pulmonary scedosporiosis or disseminated fusariosis.** *Antimicrob Agents Chemother.* 2020; **64**(3): e01735-19.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

14. Gebremariam T, Alkhazraji S, Alqarihi A, *et al.*: **Fosmanogepix (APX001) is Effective in the Treatment of Pulmonary Murine Mucormycosis Due to** *Rhizopus arrhizus.* *Antimicrob Agents Chemother.* 2020; **64**(6): e00178-20.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

15. Mansbach R, Shaw KJ, Hodges M, *et al.*: **Absorption, distribution, and excretion of ¹⁴C-APX001 after single-dose administration to rats and monkeys.** *Open Forum Infect Dis.* 2017; **4**(suppl_1): S472.
    Publisher Full Text | **Free Full Text**

16. Zhao M, Lepak AJ, Vanscoy B, *et al.*: *In Vivo* **Pharmacokinetics and Pharmacodynamics of APX001 against** *Candida* **spp. in a Neutropenic Disseminated Candidiasis Mouse Model.** *Antimicrob Agents Chemother.* 2018; **62**(4): 1–9.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

17. Hodges MR, Ople E, Shaw KJ, *et al.*: **Phase 1 Study to Assess Safety, Tolerability and Pharmacokinetics of Single and Multiple Oral Doses of APX001 and to Investigate the Effect of Food on APX001 Bioavailability.** *Open Forum Infect Dis.* 2017; **4**(suppl_1): S534.
    Publisher Full Text

18. Wring SA, Randolph R, Park SH, *et al.*: **Preclinical pharmacokinetics and pharmacodynamic target of SCY-078, a first-in-class orally active antifungal glucan synthesis inhibitor, in murine models of disseminated candidiasis.** *Antimicrob Agents Chemother.* 2017; **61**(4): e02068-16.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

19. Ghannoum M, Long L, Isham N, *et al.*: **Activity of a Novel 1,3-Beta-D-Glucan Synthase Inhibitor, Ibrexafungerp (Formerly SCY-078), against** *Candida glabrata.* *Antimicrob Agents Chemother.* 2019; **63**(12): e01510-19.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

20. Berkow EL, Angulo D, Lockhart SR: *In Vitro* **Activity of a Novel Glucan Synthase Inhibitor, SCY-078, against Clinical Isolates of** *Candida auris.* *Antimicrob Agents Chemother.* 2017; **61**(7): e00435-17.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

21. Scorneaux B, Angulo D, Borroto-Esoda K, *et al.*: **SCY-078 Is Fungicidal against** *Candida* **Species in Time-Kill Studies.** *Antimicrob Agents Chemother.* 2017; **61**(3): e01961-16.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

22. Nunnally NS, Etienne KA, Angulo D, *et al.*: *In Vitro* **Activity of Ibrexafungerp, a Novel Glucan Synthase Inhibitor against** *Candida glabrata* **Isolates with** *FKS* **Mutations.** *Antimicrob Agents Chemother.* 2019; **63**(11): e01692-19.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

23. Pfaller MA, Messer SA, Rhomberg PR, *et al.*: **Differential Activity of the Oral**

Glucan Synthase Inhibitor SCY-078 against Wild- Type and Echinocandin-Resistant Strains of *Candida* Species. *Antimicrob Agents Chemother.* 2017; **61**(8): e00161–17.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

24. Zhu YC, Barat SA, Borroto-Esoda K, *et al.*: **Pan-resistant *Candida auris* Isolates from the Outbreak in New York are Susceptible to Ibrexafungerp (A Glucan Synthase Inhibitor).** *Int J Antimicrob Agents.* 2020; **55**(4): 105922.
PubMed Abstract | **Publisher Full Text**

25. Arendrup MC, Jørgensen KM, Hare RK, *et al.*: *In Vitro* Activity of Ibrexafungerp (SCY-078) against *Candida auris* Isolates as Determined by EUCAST Methodology and Comparison with Activity against *C. albicans* and *C. glabrata* and with the Activities of Six Comparator Agents. *Antimicrob Agents Chemother.* 2020; **64**(3): e02136-19.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

26. Larkin E, Hager C, Chandra J, *et al.*: **The Emerging Pathogen *Candida auris*: Growth Phenotype, Virulence Factors, Activity of Antifungals, and Effect of SCY-078, a Novel Glucan Synthesis Inhibitor, on Growth Morphology and Biofilm Formation.** *Antimicrob Agents Chemother.* 2017; **61**(5): e02396-16.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

27. Ghannoum M, Long L, Larkin EL, *et al.*: **Evaluation of the antifungal activity of the novel oral glucan synthase inhibitor SCY-078, singly and in combination, for the treatment of invasive aspergillosis.** *Antimicrob Agents Chemother.* 2018; **62**(6): e00244-18.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

28. Spec A, Pullman J, Thompson GR, *et al.*: **MSG-10: a Phase 2 study of oral ibrexafungerp (SCY-078) following initial echinocandin therapy in non-neutropenic patients with invasive candidiasis.** *J Antimicrob Chemother.* 2019; **74**(10): 3056–3062.
PubMed Abstract | **Publisher Full Text**

29. Torrado JJ, Serrano DR, Uchegbu IF: **The oral delivery of Amphotericin B.** *Ther Deliv.* 2013; **4**(1): 9–12.
PubMed Abstract | **Publisher Full Text**

30. Seyedmousavi S, Chang YC, Law D, *et al.*: **Efficacy of Olorofim (F901318) against *Aspergillus fumigatus, A. nidulans,* and *A. tanneri* in Murine Models of Profound Neutropenia and Chronic Granulomatous Disease.** *Antimicrob Agents Chemother.* 2019; **63**(6): e00129-19.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

31. Negri CE, Johnson A, McEntee L, *et al.*: **Pharmacodynamics of the Novel Antifungal Agent F901318 for Acute Sinopulmonary Aspergillosis Caused by *Aspergillus flavus*.** *J Infect Dis.* 2018; **217**(7): 1118–1127.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

32. Lamoth F, Alexander BD: **Antifungal activities of SCY-078 (MK-3118) and standard antifungal agents against clinical non-*Aspergillus* mold isolates.** *Antimicrob Agents Chemother.* 2015; **59**(7): 4308–4311.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

33. Petraitis V, Kavaliauskas P, Planciuniene R, *et al.*: *In vitro* Activity of SCY-078 in Combination with Isavuconazole or Amphotericin B against Medically Important Moulds Conclusions / Summary. In: *American Society of Microbiology (ASM) Microbe.* Atlanta, Georgia; 2018: 498.
Reference Source

34. Wiederhold NP, Najvar LK, Jaramillo R, *et al.*: **Oral glucan synthase inhibitor SCY-078 is effective in an experimental murine model of invasive candidiasis caused by WT and echinocandin-resistant *Candida glabrata*.** *J Antimicrob Chemother.* 2018; **73**(2): 448–451.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

35. Ghannoum M, Long L, Hager C, *et al.*: **Efficacy of Oral Ibrexafungerp (IBX, Formerly SCY-078) in the Treatment of Candida auris Infection in a Murine Disseminated Model.** In: *American Society of Microbiology (ASM).* San Francisco, California; 2019: AAR-633.

36. Borroto-Esoda K, Barat S, Angulo D, *et al.*: **SCY-078 Demonstrates Significant Antifungal Activity in a Murine Model of Invasive Aspergillosis.** *Open Forum Infect Dis.* 2017; **4**(suppl_1): S472.
Publisher Full Text | **Free Full Text**

37. Petraitis V, Petraitiene R, Katragkou A, *et al.*: **Combination therapy with ibrexafungerp (formerly SCY-078), a first-in-class triterpenoid inhibitor of (1-3)-β-D-glucan synthesis, and isavuconazole for treatment of experimental invasive pulmonary aspergillosis.** *Antimicrob Agents Chemother.* 2020; **64**(6): e02429-19.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

38. Barat S, Borroto-Esoda K, Ashbaugh A, *et al.*: **Efficacy of ibrexafungerp (formerly SCY-078) against Pneumocystis pneumonia in a murine therapeutic model.** In: *29th European Congress of Clinical Microbiology and Infectious Diseases.* Amsterdam, Netherlands; 2019: O0733.
Reference Source

39. Davis MR, Donnelley MA, Thompson GR: **Ibrexafungerp: A novel oral glucan synthase inhibitor.** *Med Mycol.* 2020; **58**(5): 579–592.
PubMed Abstract | **Publisher Full Text**

40. Wring S, Borroto-Esoda K, Solon E, *et al.*: **SCY-078, a novel fungicidal agent, demonstrates distribution to tissues associated with fungal infections during mass balance studies with intravenous and oral [¹⁴C]SCY-078 in albino and pigmented rats.** *Antimicrob Agents Chemother.* 2019; **63**(2): e02119-18.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

41. Lepak AJ, Marchillo K, Andes DR: **Pharmacodynamic target evaluation of a novel oral glucan synthase inhibitor, SCY-078 (MK-3118), using an *in vivo* murine invasive candidiasis model.** *Antimicrob Agents Chemother.* 2015; **59**(2): 1265–1272.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

42. Wring S, Murphy G, Atiee G, *et al.*: **Clinical Pharmacokinetics and Drug-Drug Interaction Potential for Coadministered SCY-078, an Oral Fungicidal Glucan Synthase Inhibitor, and Tacrolimus.** *Clin Pharmacol Drug Dev.* 2019; **8**(1): 60–69.
PubMed Abstract | **Publisher Full Text**

43. Cornely OA, Ostrosky-Zeichner L, Miller R, *et al.*: **Interim Analysis of a Phase 3 Open-label Study to Evaluate the Efficacy and Safety of Oral Ibrexafungerp (formerly SCY-078) in Patients with Refractory or Intolerant Fungal Diseases (FURI).** In: *American Society of Microbiology (ASM).* San Francisco, California; 2019: CIV-166.

44. Nyirjesy P, Cadet R, Tufa M, *et al.*: **Phase 2b, Dose-Finding Study Evaluating Oral Ibrexafungerp vs Fluconazole in Vulvovaginal Candidiasis (DOVE).** In: *American College of Obstetrics & Gynecology Annual Meeting.* Nashville, TN; 2019.
Publisher Full Text

45. Juneja D, Singh O, Tarai B, *et al.*: **Successful Treatment of Two Patients with Candida auris Candidemia with the Investigational Agent, Oral Ibrexafungerp (formerly SCY-078) from the CARES Study.** In: *29th European Congress of Clinical Microbiology and Infectious Diseases.* Amsterdam, Netherlands; 2019: L0028.
Reference Source

46. Sofjan AK, Mitchell A, Shah DN, *et al.*: **Rezafungin (CD101), a next-generation echinocandin: A systematic literature review and assessment of possible place in therapy.** *J Glob Antimicrob Resist.* 2018; **14**: 58–64.
PubMed Abstract | **Publisher Full Text**

47. Pfaller MA, Carvalhaes C, Messer SA, *et al.*: **Activity of a long-acting echinocandin, rezafungin, and comparator antifungal agents tested against contemporary invasive fungal isolates (SENTRY program, 2016 to 2018).** *Antimicrob Agents Chemother.* 2020; **64**(4): e00099-20.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

48. Tóth Z, Forgács L, Locke JB, *et al.*: *In vitro* activity of rezafungin against common and rare Candida species and *Saccharomyces cerevisiae.* *J Antimicrob Chemother.* 2019; **74**(12): 3505–3510.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

49. Wiederhold NP, Locke JB, Daruwala P, *et al.*: **Rezafungin (CD101) demonstrates potent *in vitro* activity against *Aspergillus*, including azole-resistant *Aspergillus fumigatus* isolates and cryptic species.** *J Antimicrob Chemother.* 2018; **73**(11): 3063–3067.
PubMed Abstract | **Publisher Full Text**

50. Ong V, Hough G, Schlosser M, *et al.*: **Preclinical Evaluation of the Stability, Safety, and Efficacy of CD101, a Novel Echinocandin.** *Antimicrob Agents Chemother.* 2016; **60**(11): 6872–6879.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

51. Hager CL, Larkin EL, Long LA, *et al.*: **Evaluation of the efficacy of rezafungin, a novel echinocandin, in the treatment of disseminated *Candida auris* infection using an immunocompromised mouse model.** *J Antimicrob Chemother.* 2018; **73**(8): 2085–2088.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

52. Cushion M, Ashbaugh A: **Rezafungin Prophylactic Efficacy in a Mouse Model of *Pneumocystis* Pneumonia.** *Biol Blood Marrow Transplant.* 2019; **25**(3): S366.
Publisher Full Text

53. Miesel L, Lin KY, Ong V: **Rezafungin treatment in mouse models of invasive candidiasis and aspergillosis: Insights on the PK/PD pharmacometrics of rezafungin efficacy.** *Pharmacol Res Perspect.* 2019; **7**(6): e00546.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

54. Lepak AJ, Zhao M, VanScoy B, *et al.*: **Pharmacodynamics of a long-acting echinocandin, CD101, in a neutropenic invasive-candidiasis murine model using an extended-interval dosing design.** *Antimicrob Agents Chemother.* 2018; **62**(2): 1–10.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

55. Sandison T, Ong V, Lee J, *et al.*: **Safety and Pharmacokinetics of CD101 IV, a Novel Echinocandin, in Healthy Adults.** *Antimicrob Agents Chemother.* 2017; **61**(2): e01627-16.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

56. Thompson GR, Soriano A, Skoutelis A, *et al.*: **Rezafungin versus Caspofungin in a Phase 2, Randomized, Double-Blind Study for the Treatment of Candidemia and Invasive Candidiasis- The STRIVE Trial.** *Clin Infect Dis.* 2021; **73**(11): e3647–e3655.
PubMed Abstract | **Publisher Full Text**

57. Aigner M, Lass-Flörl C: **Encochleated amphotericin B: Is the oral availability of amphotericin B finally reached?** *J Fungi (Basel).* 2020; **6**(2): 66.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

58. Delmas G, Park S, Chen ZW, *et al.*: **Efficacy of orally delivered cochleates containing amphotericin B in a murine model of aspergillosis.** *Antimicrob Agents Chemother.* 2002; **46**(8): 2704–2707.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

59. Zarif L, Graybill JR, Perlin D, *et al.*: **Antifungal activity of amphotericin B cochleates against *Candida albicans* infection in a mouse model.** *Antimicrob Agents Chemother.* 2000; **44**(6): 1463–1469.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

60. Santangelo R, Paderu P, Delmas G, *et al.*: **Efficacy of oral cochleate-amphotericin B in a mouse model of systemic candidiasis.** *Antimicrob Agents Chemother.* 2000; **44**(9): 2356–2360.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

61. Lu R, Hollingsworth C, Qiu J, *et al.*: **Efficacy of oral encochleated amphotericin B in a mouse model of cryptococcal meningoencephalitis.** *mBio.* 2019; **10**(3): e00724-19.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

62. Segarra I, Movshin DA, Zarif L: **Pharmacokinetics and tissue distribution after intravenous administration of a single dose of amphotericin B cochleates, a new lipid-based delivery system.** *J Pharm Sci.* 2002; **91**(8): 1827–1837.
PubMed Abstract | **Publisher Full Text**

63. Biederdorf F, Breithaupt I, Mannino R, *et al.*: **Oral Administration of Amphotericin B (CAmB) in Humans: a Phase I Study of Tolerability and Pharmacokinetics.**
Reference Source

64. Clinicaltrials.gov: **Safety and Efficacy of Oral Encochleated Amphotericin B (CAMB/MAT2203) in the Treatment of Vulvovaginal Candidiasis (VVC).** Accessed July 9, 2020.
Reference Source

65. Hoekstra WJ, Garvey EP, Moore WR, *et al.*: **Design and optimization of highly-selective fungal CYP51 inhibitors.** *Bioorganic Med Chem Lett.* 2014; **24**(15): 3455–3458.
PubMed Abstract | **Publisher Full Text**

66. Schell WA, Jones AM, Garvey EP, *et al.*: **Fungal CYP51 Inhibitors VT-1161 and VT-1129 Exhibit Strong *In Vitro* Activity against *Candida glabrata* and *C. krusei* Isolates Clinically Resistant to Azole and Echinocandin Antifungal Compounds.** *Antimicrob Agents Chemother.* 2017; **61**(3): e01817-16.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

67. Nishimoto AT, Wiederhold NP, Flowers SA, *et al.*: ***In vitro* activities of the novel investigational tetrazoles VT-1161 and VT-1598 compared to the triazole antifungals against azole-resistant strains and clinical isolates of *Candida albicans*.** *Antimicrob Agents Chemother.* 2019; **63**(6): e00341-19.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

68. Wiederhold NP, Patterson HP, Tran BH, *et al.*: **Fungal-specific Cyp51 inhibitor VT-1598 demonstrates *in vitro* activity against *Candida* and *Cryptococcus* species, endemic fungi, including *Coccidioides* species, *Aspergillus* species and *Rhizopus arrhizus*.** *J Antimicrob Chemother.* 2018; **73**(2): 404–408.
PubMed Abstract | **Publisher Full Text**

69. Garvey EP, Sharp AD, Warn PA, *et al.*: **The novel fungal CYP51 inhibitor VT-1598 displays classic dose-dependent antifungal activity in murine models of invasive aspergillosis.** *Med Mycol.* 2020; **58**(4): 505–513.
PubMed Abstract | **Publisher Full Text**

70. Wiederhold NP, Lockhart SR, Najvar L, *et al.*: **The Fungal Cyp51-Specific Inhibitor VT-1598 Demonstrates *In Vitro* and *In Vivo* Activity against *Candida auris*.** *Antimicrob Agents Chemother.* 2019; **63**(3): e02233-18.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

71. Shubitz LF, Trinh HT, Galgiani JN, *et al.*: **Evaluation of VT-1161 for treatment of coccidioidomycosis in murine infection models.** *Antimicrob Agents Chemother.* 2015; **59**(12): 7249–7254.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

72. Gebremariam T, Alkhazraji S, Lin L, *et al.*: **Prophylactic Treatment with VT-1161 Protects Immunosuppressed Mice from *Rhizopus arrhizus* var. *arrhizus* Infection.** *Antimicrob Agents Chemother.* 2017; **61**(9): e00390-17.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

73. Wiederhold NP, Shubitz LF, Najvar LK, *et al.*: **The novel fungal Cyp51 inhibitor VT-1598 is efficacious in experimental models of central nervous system coccidioidomycosis caused by *Coccidioides posadasii* and *Coccidioides immitis*.** *Antimicrob Agents Chemother.* 2018; **62**(4): e02258-17.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

74. Brand SR, Degenhardt TP, Person K, *et al.*: **A phase 2, randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy and safety of orally administered VT-1161 in the treatment of recurrent vulvovaginal candidiasis.** *Am J Obstet Gynecol.* 2018; **218**(624): 624.e1–624.e9.
PubMed Abstract | **Publisher Full Text**

75. Elewski B, Brand S, Degenhardt T, *et al.*: **A Phase 2, randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy and safety of VT-1161 oral tablets in the treatment of patients with distal and lateral subungual onychomycosis of the toenail.** *Br J Dermatol.* 2020.
PubMed Abstract | **Publisher Full Text**

76. Rodvold KA, George JM, Yoo L: **Penetration of anti-infective agents into pulmonary epithelial lining fluid: Focus on antibacterial agents.** *Clin Pharmacokinet.* 2011; **50**(10): 637–64.
PubMed Abstract | **Publisher Full Text**

77. Colley T, Alanio A, Kelly SL, *et al.*: ***In Vitro* and *In Vivo* Antifungal Profile of a Novel and Long-Acting Inhaled Azole, PC945, on *Aspergillus fumigatus* Infection.** *Antimicrob Agents Chemother.* 2017; **61**(5): e02280-16.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

78. Rudramurthy SM, Colley T, Abdolrasouli A, *et al.*: ***In vitro* antifungal activity of a novel topical triazole PC945 against emerging yeast *Candida auris*.** *J Antimicrob Chemother.* 2019; **74**(10): 2943–2949.
PubMed Abstract | **Publisher Full Text**

79. Hope WW, Kruhlak MJ, Lyman CA, *et al.*: **Pathogenesis of *Aspergillus fumigatus* and the Kinetics of Galactomannan in an *In Vitro* Model of Early Invasive Pulmonary Aspergillosis: Implications for Antifungal Therapy.** *J Infect Dis.* 2007; **195**(3): 455–466.
PubMed Abstract | **Publisher Full Text**

80. Colley T, Sehra G, Daly L, *et al.*: **Antifungal synergy of a topical triazole, PC945, with a systemic triazole against respiratory *Aspergillus fumigatus* infection.** *Sci Rep.* 2019; **9**(1): 9482.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

81. Kimura G, Nakaoki T, Colley T, *et al.*: ***In vivo* biomarker analysis of the effects of intranasally dosed PC945, a novel antifungal triazole, on *Aspergillus fumigatus* infection in immunocompromised mice.** *Antimicrob Agents Chemother.* 2017; **61**(9): e00124-17.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

82. Pagani N, Armstrong-James D, Reed A: **Successful salvage therapy for fungal bronchial anastomotic infection after -lung transplantation with an inhaled triazole anti-fungal PC945.** *J Hear Lung Transplant.* 2020; **39**(12): 1505–1506.
PubMed Abstract | **Publisher Full Text**

83. Oliver JD, Sibley GEM, Beckmann N, *et al.*: **F901318 represents a novel class of antifungal drug that inhibits dihydroorotate dehydrogenase.** *Proc Natl Acad Sci U S A.* 2016; **113**(45): 12809–12814.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

84. Wiederhold NP, Najvar LK, Jaramillo R, *et al.*: **The Orotomide Olorofim Is Efficacious in an Experimental Model of Central Nervous System Coccidioidomycosis.** *Antimicrob Agents Chemother.* 2018; **62**(9): e00999-18.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

85. Buil JB, Rijs AJMM, Meis JF, *et al.*: ***In vitro* activity of the novel antifungal compound F901318 against difficult-to-treat *Aspergillus* isolates.** *J Antimicrob Chemother.* 2017; **72**(9): 2548–2552.
PubMed Abstract | **Publisher Full Text**

86. Wiederhold NP, Law D, Birch M: **Dihydroorotate dehydrogenase inhibitor F901318 has potent *in vitro* activity against *Scedosporium* species and *Lomentospora* prolificans.** *J Antimicrob Chemother.* 2017; **72**(7): 1977–1980.
PubMed Abstract | **Publisher Full Text**

87. Biswas C, Law D, Birch M, *et al.*: ***In vitro* activity of the novel antifungal compound F901318 against Australian *Scedosporium* and *Lomentospora* fungi.** *Med Mycol.* 2018; **56**(8): 1050–1054.
PubMed Abstract | **Publisher Full Text**

88. Kirchhoff L, Dittmer S, Weisner AK, *et al.*: **Antibiofilm activity of antifungal drugs, including the novel drug olorofim, against *Lomentospora prolificans*.** *J Antimicrob Chemother.* 2020; **75**(8): 2133–2140.
PubMed Abstract | **Publisher Full Text**

89. Jorgensen KM, Astvad KMT, Hare RK, *et al.*: **EUCAST Determination of Olorofim (F901318) Susceptibility of Mold Species, Method Validation, and MICs.** *Antimicrob Agents Chemother.* 2018; **62**(8): e00487-18.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

90. Kirchhoff L, Dittmer S, Buer J, *et al.*: ***In vitro* activity of olorofim (F901318) against fungi of the genus, *Scedosporium* and *Rasamsonia* as well as against *Lomentospora prolificans, Exophiala dermatitidis* and azole-resistant *Aspergillus fumigatus*.** *Int J Antimicrob Agents.* 2020; **56**(3): 106105.
PubMed Abstract | **Publisher Full Text**

91. Hope WW, McEntee L, Livermore J, *et al.*: **Pharmacodynamics of the Orotomides against *Aspergillus fumigatus*: New Opportunities for Treatment of Multidrug-Resistant Fungal Disease.** *mBio.* 2017; **8**(4): e01157-17.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

92. du Pré S, Beckmann N, Almeida MC, *et al.*: **Effect of the Novel Antifungal Drug F901318 (Olorofim) on Growth and Viability of Aspergillus fumigatus.** *Antimicrob Agents Chemother.* 2018; **62**(8): e00231-18.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

93. Kennedy T, Allen G, Steiner J, *et al.*: **Multiple Dose Pharmacokinetics of an Immediate-Release Tablet Formulation of F901318 in Healthy Male and Female Subjects.** In: *European Congress of Clinical Microbiology and Infectious Diseases.* Vienna, Austria; 2017; P1710.
Reference Source

94. Kennedy T, Graham A, Steiner J, *et al.*: **An open-label study in healthy volunteers to evaluate the potential for cytochrome P450 3A4 inhibition by F901318 using oral midazolam as a probe.** In: *European Congress of Clinical Microbiology and Infectious Diseases.* Vienna, Austria; 2017; P1737.
Reference Source

F1000Research

Open Peer Review

Current Peer Review Status: ✓ ✓

Version 2

Reviewer Report 24 January 2022

https://doi.org/10.5256/f1000research.119851.r119566

✓ **Shahram Mahmoudi** ⓘD

Department of Parasitology and Mycology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

I have no further comments to make.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Medical Mycology, Antifungal Drugs

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 02 December 2021

https://doi.org/10.5256/f1000research.31334.r99295

? **Shahram Mahmoudi** ⓘD

Department of Parasitology and Mycology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

The study by Jacobs et al. summarizes the antifungal drugs in clinical trials. The corresponding author is experienced, the study is well written, and when looked alone, it seems perfect.

However, I think the following points need to be considered by the authors:
- ○ Please be consistent in the use of units. In some cases, the unites are linked to the numbers (e.g. 35mg/L), and in the rest are separated by a space (e.g. 35 mg/L). Please add one space between numbers and units throughout the manuscript.

- ○ In my opinion, conclusion needs to be changed as in its current form it looks like the aim of study and not a conclusion.

Is the topic of the review discussed comprehensively in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Medical Mycology, Antifungal Drugs

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 27 Dec 2021

Samantha Jacobs, Icahn School of Medicine, New York, USA

Response to Reviewer #2 Comments
12.27.2021
The study by Jacobs et al. summarizes the antifungal drugs in clinical trials. The corresponding author is experienced, the study is well written, and when looked alone, it seems perfect.

However, I think the following points need to be considered by the authors:
- ○ Please be consistent in the use of units. In some cases, the unites are linked to the numbers (e.g. 35mg/L), and in the rest are separated by a space (e.g. 35 mg/L). Please add one space between numbers and units throughout the manuscript.

Author response: We have added one space between numbers and units throughout the manuscript.
- ○ In my opinion, conclusion needs to be changed as in its current form it looks like the

> aim of study and not a conclusion
>
> **Author response**: We have modified the conclusion as suggested by the reviewer to summarize and highlight the advantages of the most promising investigational agents discussed in the manuscript.
>
> ***Competing Interests:*** No competing interests were disclosed.

Reviewer Report 23 July 2021

https://doi.org/10.5256/f1000research.31334.r89343

✔ **Charalampos Antachopoulos** [iD]

Third Department of Pediatrics, Faculty of Medicine, School of Health Sciences, Hippokration General Hospital, Aristotle University, Thessaloniki, Greece

This is a well-written and comprehensive paper summarizing recent data on novel antifungal agents in clinical development. Table 1 is very helpful. I have only few minor comments:

1. Abstract: consider change "we examine" to: "we review / present / discuss".

2. Fosmanogepix: please provide more specific *in vitro* data on species (rather than genera) susceptibility for *Aspergillus* spp, *Fusarium* spp and *Scedosporium* spp.

3. *In vitro* antifungal activity of fosmanogepix: it should be mentioned that MEC rather than MIC is determined for assessment of activity against molds.

4. "Fosmanogepix also has activity against fungi in the order Mucorales (MIC ranges of 1 to 8 µg/mL)": please provide reference for this statement; is the term MIC correct or should it be replaced by MEC?

5. "Ibrexafungerp has fungistatic activity against *Aspergillus* species (MIC range <0.06 µg/mL to 32 µg/mL...)": in the reference cited by the authors (ref. 25, Ghannoum et al, AAC 2018), ibrexafungerp *in vitro* activity against *Aspergillus* had been determined using both MEC and MIC; the MIC values tended to be 8-fold higher than correspondent MEC values. Please modify the text accordingly.

6. Are there data on the *in vitro* activity of ibrexafungerp and rezafungin against *Candida parapsilosis* in comparison with other *Candida* species?

7. What is the published evidence for PK/PD indices associated with therapeutic outcome for each one of the novel antifungal agents presented in this paper?

8. Conclusion: the content of the conclusion paragraph would fit more for an introduction rather than a wrap-up of the main findings. I suggest to significantly modify this section, in order to briefly mention the novel agents in clinical development and their selective advantages compared to our current antifungal armamentarium.

Is the topic of the review discussed comprehensively in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: 1. Antifungal agents (in vitro activity against planktonic fungal cells or biofilms); 2. Host immune responses against fungal infections; 3. Pharmacokinetics and safety of novel antimicrobial agents in pediatric patients

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 27 Dec 2021

Samantha Jacobs, Icahn School of Medicine, New York, USA

Response to Reviewer #1 Comments
12.27.2021

This is a well-written and comprehensive paper summarizing recent data on novel antifungal agents in clinical development. Table 1 is very helpful. I have only few minor comments:

1. Abstract: consider change "we examine" to: "we review / present / discuss".
Author response: We have changed the wording to "We discuss…"

2. Fosmanogepix: please provide more specific *in vitro* data on species (rather than genera) susceptibility for *Aspergillus* spp, *Fusarium* spp and *Scedosporium* spp.
Author response: We have specified the *in vitro* activity of fosmanogepix to the species level including representative MEC values.

3. In vitro antifungal activity of fosmanogepix: it should be mentioned that MEC rather than

MIC is determined for assessment of activity against molds.
Author response: We have added a line noting this distinction.

4. "Fosmanogepix also has activity against fungi in the order Mucorales (MIC ranges of 1 to 8 µg/mL)": please provide reference for this statement; is the term MIC correct or should it be replaced by MEC?**Author response**: We have added the reference for this statement (reference #2). Indeed, the manuscript, published in 2011, used MIC rather the MEC determination for activity of fosmanogepix against *R. oryzae* and *R. microsporus*. We have also added another reference that reports MEC values (reference #3).

5. "Ibrexafungerp has fungistatic activity against *Aspergillus* species (MIC range <0.06 µg/mL to 32 µg/mL...)": in the reference cited by the authors (ref. 25, Ghannoum et al, AAC 2018), ibrexafungerp *in vitro* activity against *Aspergillus* had been determined using both MEC and MIC; the MIC values tended to be 8-fold higher than correspondent MEC values. Please modify the text accordingly.
Author response: Thank you for your comment. We have modified the text to report the MEC rather than MIC determinations for ibrexafungerp against *Aspergillus* species.

6. Are there data on the *in vitro* activity of ibrexafungerp and rezafungin against *Candida parapsilosis* in comparison with other *Candida* species?
Author response: Thank you for your question. The *in vitro* activity of ibrexafungerp against *C. parapsilosis* is comparable or more potent than that of echinocandins. The MICs against *C. parapsilosis* are generally similar to those of other *Candida* species. For rezafungin, the *in vitro* activity against *C. parapsilosis* is less potent than against other common *Candida* species causing disease. These data are added to the text.

7. What is the published evidence for PK/PD indices associated with therapeutic outcome for each one of the novel antifungal agents presented in this paper?
Author response: For fosmanogepix, ibrexafungerp, rezafungin, and olorofim, we have included the key PK/PD indices associated with therapeutic outcome in experimental animal models as there are insufficient clinical data to determine this information. We have also created an additional table (Table 2) to highlight this information.

8. Conclusion: the content of the conclusion paragraph would fit more for an introduction rather than a wrap-up of the main findings. I suggest to significantly modify this section, in order to briefly mention the novel agents in clinical development and their selective advantages compared to our current antifungal armamentarium.
Author response: We have modified the conclusion as suggested by the reviewer to summarize and highlight the advantages of the most promising investigational agents discussed in the manuscript.

Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias

- You can publish traditional articles, null/negative results, case reports, data notes and more

- The peer review process is transparent and collaborative

- Your article is indexed in PubMed after passing peer review

- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research